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Development of fear acquisition and extinction in children: Effects of age and anxiety

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ABSTRACT

Development of anxiety disorders is associated with neurobiological changes in areas that are a critical part of the fear neurocircuitry. Fear conditioning paradigms can offer insight into the mechanisms underlying the neurobiological ontogeny of anxiety. A small number of studies have focused on the effects of age and anxiety separately in school age children. The present study aimed to investigate these effects in 8–13 year old children with higher and lower trait anxiety. We examined differential fear conditioning and extinction using skin conductance responses and fear-potentiated startle in 60 children recruited from a low-income urban population. The results indicated that children under 10 years of age show poor discrimination of conditioned stimuli, and that anxiety increases fear responses during fear acquisition. After controlling for age and trauma exposure, fear-potentiated startle to the safety cue predicted child anxiety levels suggesting that impaired safety signal learning may be a risk factor for anxiety disorders in adulthood. Identifying risk phenotypes in children may provide opportunities for early intervention and prevention of illness.

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1. Introduction

The prevalence of anxiety disorders is known to increase during late childhood and early adolescence, suggesting that this period may be developmentally critical in identifying individuals at risk for adult anxiety (Cohen, Cohen, & Brook, 1993). A recent review of development of brain structures in children at risk for anxiety reported dysfunction in amygdala and prefrontal regions associated with anxiety (Blackford & Pine, 2012). In addition, anxiety disorders are associated with larger amygdala volume in children and adolescents (De Bellis et al., 2000). Given that these neurobiological changes are observed in areas that are a critical part of the fear neurocircuitry (Whalen, 1998), fear conditioning paradigms can offer insight into the mechanisms underlying the neurobiological ontogeny of anxiety (Britton, Lissek, Grillon, Norcross, & Pine, 2011). In human fear conditioning experiments, the two most commonly used peripheral measures of fear are an increase in skin conductance response (SCR) and fear-potentiated startle. Skin conductance, which reflects changes in sweat gland activity that alters the electrical conductivity of the skin, is a direct index of sympathetic nervous system activation, and an excellent peripheral metric for arousal. Importantly, the magnitude of the SCR reliably increases during presentations of a reinforced conditioned stimulus (CS+) that was previously paired with an aversive unconditioned stimulus (US), making it a good index of conditioned fear (Pattwell et al., 2012; Waters, Henry, & Neumann, 2009). In fear-potentiated startle, the magnitude of the startle reflex increases during aversive CS presentations (Glenn et al., 2011; Grillon & Davis, 1997; Jovanovic et al., 2010), a phenomenon that has been extensively modelled in animals (Davis, 1992; Falls & Davis, 1994). In fear extinction paradigms, the stimulus that was previously paired with the US (that is, the CS+) is then repeatedly presented without the US, so that it no longer elicits a fear response (Quirk, 2006). Whereas fear acquisition refers to learning that something is dangerous, extinction is a mechanism by which an individual learns that something that was previously dangerous has become safe. Neuroimaging studies in humans have implicated the amygdala activation during fear conditioning (Phan, Wager, Taylor, & Liberzon, 2002) and amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC) activation in fear extinction (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Milad et al., 2007).

A small number of studies have investigated developmental trends in activity in the above neural structures. One study used functional magnetic resonance imaging (fMRI) during fear

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conditioning in adolescents and adults, and found that compared to adults, the CS+ evoked greater responses in the amygdala and hippocampus relative to the CS− in adolescents (Lau et al., 2011). Although no other studies specifically examined fear conditioning using fMRI in children and adolescents, several studies have used fear-relevant cues, such as fearful faces, to activate these structures. For example, a recent study found a developmental shift in functional connectivity between the amygdala and the medial prefrontal cortex (mPFC) during the viewing of fearful faces (Gee et al., 2013). The cross-sectional study included children from 4 years of age to adults and found that these areas were positively connected prior to age 10 years, and negatively connected after age 10 years (Gee et al., 2013).

Similar age effects have been found in a fear conditioning studies using fear potentiation of the acoustic startle response with faces as CSs and the sound of a woman's scream as the aversive US that was paired to one face (CS+), but not a second face (CS−). The study found that fear-potentiated startle to the CS+ was greater in the 10–13 year old group compared to the 8–9 year olds (Glenn et al., 2011). Furthermore, the study suggested that generalized fear responses to safety cues occurs around age 10, since children in the 8–9 age group showed higher responses to the CS− and poor generalization between the CS+ face and a generalization stimulus face. A developmental study of extinction examined SCR in children, adolescents, and adults and found normal (adult-like) levels of extinction to the CS+ in children (Pattwell et al., 2012). Interestingly, adolescent showed suppressed extinction compared to both children and adults (Pattwell et al., 2012). The results of this study indicated that there may be a reduction in extinction during this developmental stage due to a lack of synaptic plasticity in the vmPFC. It is also possible that hormonal changes during puberty impact extinction, as data from animal and human studies suggest that estrogen levels play a role in extinction (Glover et al., 2012; Zeidan et al., 2011).

A very small number of studies have examined the effect of anxiety on fear conditioned responses in children. Waters and colleagues included anxious and non-anxious children between 8 and 12 years of age in their study of fear conditioning, using a loud tone as the US. Anxious children showed greater fear responses to all CSs during conditioning compared to controls, and did not discriminate between danger (CS+) and safety (CS−) signals on SCR. A similar fear conditioning study using the scream US found that pediatric anxiety was associated with higher ratings of fear to all CSs in the experiment (Lau et al., 2008). Finally, a study of fear extinction in anxious and non-anxious children found that anxious children had higher fear responses measured with fear-potentiated startle, SCR and fear ratings (Liberman, Lipp, Spence, & March, 2006). Increased fear responses may be a biomarker of risk for psychopathology: a study of adolescent offspring of adults with anxiety disorders found that these adolescents had higher fear-potentiated startle responses compared to low-risk adolescents (Grillon, Dierker, & Merikangas, 1998). More specifically, increased fear-potentiated startle in the presence of safety signals may be an early indicator of a propensity for anxiety disorders, as it has been associated with higher anxiety in adolescents who were categorized as behaviorally inhibited as toddlers (Reeb-Sutherland et al., 2009). To date, no studies have specifically examined the association between anxiety and fear responses in children under 10 years old as compared to those 10 years of age and older. Such information can point to developmental windows of opportunity for early intervention.

The objective of the current study was to investigate fear acquisition and extinction using SCR and fear-potentiated startle in school-age children, focusing on the effects of age and child anxiety. Our laboratory has developed a fear conditioning paradigm which uses neutral stimuli (geometric shapes appearing on a computer monitor) as CSs and an aversive airblast to the larynx as the US (Jovanovic et al., 2005). Given our previous findings in adults with PTSD and the prior studies of children in the literature (Glenn et al., 2011), we hypothesized that children 10 years and older would show better discrimination between danger cues (CS+) and safety cues (CS−), and that higher anxiety would be associated with greater fear responses in the presence of the CS−. On the other hand, we hypothesized that older children may show reduced fear extinction as observed in studies of adolescents (Pattwell et al., 2012).

2. Material and methods

2.1. Participants

The study included 60 participants between 8 and 13 years of age (mean age = 10.3, SD = 1.58), of which 31 were female. The participants were recruited from the waiting rooms of the Primary Care or Obstetrics Gynecology clinics at the Grady Health System in Atlanta, GA. Eligible participants were between 8 and 13 years of age willing to participate; exclusion criteria were autism spectrum disorders, bipolar or psychotic disorders, or cognitive disability. The mothers and children were recruited from a low-income urban population with high trauma exposure (Jovanovic et al., 2011; Kamkwalala et al., 2012). We used the Violence Exposure Scale for Children-Revised (VEX-R) to assess the participants' exposure to traumatic events. The scale comes in a male and female version. Internal consistency ranges from 0.80 to 0.86 (Fox & Leavitt, 1995). Prior to their participation, all mothers signed informed consent as well as parental permission for their children, and the children provided study assent approved by the Emory University Institutional Review Board and the Grady Research Oversight Committee.

2.2. Psychological assessments

Anxiety in the participants was assessed using the Behavioral Assessment System for Children – Second Edition (BASC-2; Reynolds, 2004). This instrument has a parent report and child report section. This 161-item scale for children ages 6–11 encompasses 8 clinical subscales which combine to yield composite scores on 2 child psychopathology dimensions: Externalizing (Aggression, Attention Problems, Conduct Disorder, and Hyperactivity scales) and Internalizing (Anxiety, Atypicality, Depression, Somatization, and Withdrawal scales). The results are normalized by age. For the present study we focused on child-reported Anxiety ratings. Test–retest reliability, internal consistency, and convergent validity of the scales are very high (Reynolds & Kamphaus, 2004). IQ was assessed using the Reynolds Intellectual Assessment Scale (RIAS; Reynolds & Kamphaus, 2003), and participants with cognitive disabilities were excluded from further analyses. Psychological data were available for 54 participants.

2.3. Psychophysiological assessment

The psychophysiological data was collected using Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA). Electromyographic (EMG) and skin conductance (SC) data were sampled at 1000 Hz and amplified using the respective modules of the Biopac system. The acquired data were filtered, rectified, and smoothed in MindWare software (MindWare Technologies, Inc.) and exported for statistical analyses. EMG activity was recorded from two 5 mm Ag/AgCl electrodes placed over the *orbicularis oculi* muscle, approximately 1 cm under the pupil and 1 cm below the lateral canthus. The impedances for all participants were less than

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